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Anticholinergics combined with alpha-blockers for treating lower urinary tract symptoms related to benign prostatic obstruction (Protocol)

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Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD012336.

DOI: 10.1002/14651858.CD012336.

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Anticholinergics combined with alpha-blockers for treating lower urinary tract symptoms related to benign prostatic obstruction

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Editorial group: Cochrane Urology Group.

Publication status and date: New, published in Issue 9, 2016.

Citation: Pang R, Zhou XY, Wang XL, Wang B, Yin XL, Bo H. Anticholinergics combined with alpha-blockers for treating lower urinary tract symptoms related to benign prostatic obstruction. *Cochrane Database of Systematic Reviews* 2016, Issue 9. Art. No.: CD012336. DOI: 10.1002/14651858.CD012336.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of anticholinergics combined with alpha-blockers compared to placebo or other medical treatments in men with lower urinary tract symptoms (LUTS) secondary to benign prostatic obstruction (BPO).

BACKGROUND

Description of the condition

Lower urinary tract symptoms (LUTS) are a common condition in elderly men (Oelke 2013). Benign prostatic obstruction (BPO) is a main etiology for aging males to experience LUTS and it differs from benign prostatic hyperplasia (BPH) and benign prostatic enlargement (BPE). BPH is a histological diagnosis characterized by the proliferation of epithelial and stromal cells within the prostate gland (Hansen 1995). BPE refers to an increase in volume of the prostate due to BPH. BPO is an obstruction that results from BPE, which can be proven by pressure flow studies, or be highly

suspected from flow rates and if the gland is enlarged (Abrams 2013). The prevalence of BPH and LUTS rises significantly with increased age. It is estimated that 70% of men between 60 and 70 years old and 80% of men over 70 years old are affected by BPH in the USA (Wei 2005). Based on a prospective, community-based cohort study, the Rancho Bernardo study, 56% of men younger than 80 years of age, 70% of men 80 to 89 years of age, and 90% of men older than 90 years of age experience LUTS (Parsons 2008). In general, LUTS are divided into storage LUTS (increased daytime frequency, nocturia, urgency, and incontinence), voiding LUTS (slow stream, splitting or spraying, intermittent stream, hesitancy, straining, and terminal dribble), and postmicturition LUTS (feeling of incomplete emptying and postmicturition dribble) (Abrams 2002). All of these bothersome symptoms negatively impact the

public health and reduce the quality of life (QOL). Moreover, the cost related to LUTS has been a social and economic burden. During 2000, the direct treatment expenditure for LUTS related to BPO was USD 1.1 billion in the USA (Wei 2008). Based on Hospital Episode Statistics data (2007 to 2008), LUTS secondary to BPO have been the fifth most expensive disease to the UK National Health Service (NHS) and account for a cost of GBP 1.16 billion each year (Kirby 2010).

Description of the intervention

Alpha-adrenergic antagonists (alpha-blockers) have been considered as the first-line pharmacotherapy for men with LUTS related to BPO due to their well-documented efficacy (Gravas 2015). It is confirmed that alpha-blockers can relieve BPO by decreasing smooth muscle tone in the prostate and bladder neck (Chapple 2004). The American Urological Association (AUA) has determined that the alpha-blockers alfuzosin, doxazosin, tamsulosin, and terazosin are appropriate and effective treatment options for men with LUTS secondary to BPO (McVary 2011). Clinical studies have shown that these alpha-blockers can typically reduce the International Prostate Symptom Score (IPSS) by approximately 20% to 50% and increase the maximum urine flow (Qmax) by approximately 15% to 45% (MacDonald 2005; Wilt 2006). A study further showed that alpha-blockers could improve Qmax more effectively in younger men (less than 65 years old) as compared to older men (≥ 65 years old) (Novara 2015). Adverse effects of alpha-blockers include postural hypotension, dizziness, headache, asthenia, syncope, peripheral edema, and retrograde ejaculation, which cause approximately 4% to 10% of patients to withdraw from alpha-blocker treatment (Djavan 1999).

Anticholinergics are considered as one of the standard pharmacotherapies for people with overactive bladder (Gormley 2015). These agents can block the combination of acetylcholine and muscarinic receptors on detrusor smooth muscle, which can improve storage LUTS by relieving the detrusor overactivity (Andersson 2004; Reynard 2004). The licensed agents for treating storage LUTS include darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine, and trospium chloride (Gravas 2015). Combination therapy with an alpha-blocker and an anticholinergic can achieve synergistic effect of these two kinds of medicines by blocking both alpha-adrenergic receptors and muscarinic cholinergic receptors in the lower urinary tract. Randomized controlled trials (RCTs) (Chapple 2009; Kaplan 2006; Lee 2011; MacDiarmid 2008; van Kerrebroeck 2013; Yamaguchi 2011), and RCT-based meta-analysis (Filson 2013; Xin 2013), have provided evidence for the advantage of combination therapy in management of male storage LUTS.

How the intervention might work

Two types of alpha-adrenergic receptors, alpha-1 receptor and alpha-2 receptor, are found in human central and peripheral nervous systems. Of those, alpha-1 receptors are mainly located on the urinary bladder base and prostatic urethra (Kunisawa 1985). Three different alpha-1 receptor subtypes have been identified: alpha-1A, alpha-1B, and alpha-1D (Oelke 2013). Alpha-1A subtype primarily mediates smooth muscle tone in the prostate and bladder neck, while alpha-1B subtype generally mediates vascular smooth muscle contraction (Fine 2008). Alpha-1D subtype is believed to function as a mediator for lower urinary tract function through regulation of bladder muscle contraction and sacral spinal cord innervation (Fine 2008). Alpha-blockers can inhibit the activation of these alpha-1 receptors, which results in decreased intracellular Ca^{2+} and subsequently causes smooth muscle relaxation.

Acetylcholine is the predominant neurotransmitter in the lower urinary tract that can combine with muscarinic receptors on the surface of various cells, such as smooth muscle cells, urothelial cells, nerve cells, or epithelial cells. Five different muscarinic receptor subtypes have been identified in humans: M_1 , M_2 , M_3 , M_4 , and M_5 receptors. Of those, M_2 and M_3 subtypes primarily express on the surface of the detrusor muscle, which is involved in bladder contractions (Braverman 2006; Chess-Williams 2001). Anticholinergics can inhibit the activation of these two subtypes of muscarinic receptors, which suppresses the release of Ca^{2+} mediated by G-protein and the opening of calcium channels in cell membranes, and, consequently, results in the relaxation of the detrusor muscle.

Combination therapy with alpha-blockers and anticholinergics can inhibit alpha-adrenergic and muscarinic receptors simultaneously, which may improve LUTS related to BPO.

Why it is important to do this review

Although voiding and postmicturition LUTS are typically related to BPO (Abrams 2002), as many as 50% of men with BPO complain of storage LUTS (Reynard 2004). Alpha-blockers are considered as the first-line drug for men with LUTS secondary to BPO (Gravas 2015), but up to one third of men report no improvement in their LUTS (Djavan 1999), especially storage LUTS, after taking this agent. To relieve storage LUTS more effectively, combination therapy with alpha-blockers and anticholinergics has been tried in some clinical trials. However, the results from these studies are inconsistent due to different designs used in these studies, which causes the effect of combination therapy with alpha-blockers and anticholinergics on LUTS to be controversial. Moreover, it is reported that anticholinergics may result in urinary retention in patients with BPO (Vande Griend 2012; Zhou 2015). Additionally, the long-term effects of combination therapy with alpha-blockers and anticholinergics for LUTS related to BPO are unclear. Therefore, it is desirable to conduct a systematic review. Although two meta-analyses have shown that combination therapy is associated with greater benefit than alpha-blockers monother-

apy (Filson 2013; Xin 2013), some recent trials revealed that the addition of anticholinergics cannot further improve LUTS secondary to BPO (Ko 2014; Lee 2014). There have been no recent systematic reviews to further analyze the efficacy of combination therapy. In addition, unlike the published meta-analyses, this systematic review will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to rate the quality of the evidence.

OBJECTIVES

To assess the effects of anticholinergics combined with alpha-blockers compared to placebo or other medical treatments in men with lower urinary tract symptoms (LUTS) secondary to benign prostatic obstruction (BPO).

METHODS

Criteria for considering studies for this review

Types of studies

We will include parallel-group randomized controlled trials (RCTs). We will exclude quasi-randomized studies and observational studies (cohort, case-control and cross-sectional). We will include studies regardless of their publication status or language of publication.

Types of participants

Men with lower urinary tract symptoms (LUTS) secondary to benign prostatic obstruction (BPO) that is proven by pressure flow studies, or be highly suspected from flow rates when an enlarged prostate volume is detected (Abrams 2013), age 40 years or older, and a total International Prostate Symptom Score (IPSS) of ≥ 8 . We will exclude trials of men with a known neurogenic bladder due to spinal cord injury, multiple sclerosis, or central nervous system disease. We will also exclude studies that examine medical therapy for men who were treated with surgery for BPO.

We will include studies in which only a subset of participants are relevant to this review, if data are available separately for the relevant subset.

Types of interventions

We will perform the following comparisons:

- combination therapy with alpha-blockers (for example, doxazosin, alfuzosin, silodosin, tamsulosin, terazosin, and

naftopidil) and anticholinergics (for example, dfesoterodine, tolterodine, darifenacin, oxybutynin, propiverine, solifenacin, and trospium chloride) versus placebo;

- combination therapy with alpha-blockers and anticholinergics versus other medical treatments for LUTS related to BPO, including alpha-blockers monotherapy and anticholinergics monotherapy.

Types of outcome measures

We will not use the measurement of the outcomes assessed in this review as an eligibility criterion. We will calculate the minimally important difference for each primary outcome to aid our interpretation of the results. We will assess the primary and secondary outcomes with a follow-up of three to 12 months after intervention, if possible.

Primary outcomes

- Change in urological symptom scores, assessed with a validated scale (such as the IPSS; clinically meaningful improvement is generally considered to be \geq three points decrease in the IPSS, as defined by the American Urological Association (AUA) (AUA 2010)). For studies which only report final values, these final values will be combined with changes from baseline for meta-analysis;
- incidence of adverse events (graded as the Common Terminology Criteria for Adverse Events (CTCAE): Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening or disabling; Grade 5 = death-related; we will also consider the definition the trial authors used in each clinical trial).

Secondary outcomes

- Incidence of acute urinary retention;
- incidence of need for surgical intervention;
- change in the maximum urine flow (Q_{max}) measured by uroflowmetry. For studies that only report final values, we will combine these final values with changes from baseline for meta-analysis;
- change in the postvoid residual volume (PVR) evaluated by ultrasound. For studies that only report final values, we will combine these final values with changes from baseline for meta-analysis;
- change in quality of life (QOL), assessed with IPSS bother score (meaningful improvement is generally considered to be \geq two points decrease). For studies that only report final values, we will combine these final values with changes from baseline for meta-analysis.

Main outcomes for 'Summary of findings' table

We will present a 'Summary of findings' table and report the following outcomes, which we have listed according to priority:

- change in urological symptom scores;
- incidence of adverse effects;
- incidence of acute urinary retention;
- incidence of need for surgical intervention;
- change in Qmax measured by uroflowmetry;
- change in QOL, assessed with IPSS bother score.

Search methods for identification of studies

We will perform a comprehensive search with no restrictions on the language of publication or publication status. We plan to rerun searches within three months prior to anticipated publication of the review.

Electronic searches

We will search the following electronic sources:

- the Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library (for the search strategy, see [Appendix 1](#));
- MEDLINE via PubMed (1953 to present) ([Appendix 2](#));
- EMBASE via Elsevier (1947 to present) ([Appendix 3](#));
- Science Citation Index via Web of Science, Core Collection (1975 to present) ([Appendix 4](#));
- Conference Proceedings Citation Index via Web of Science, Core Collection (1975 to present) ([Appendix 4](#));
- CBM (Chinese Biomedical Literature Database) via SinoMed (1978 to present) (search in Chinese) ([Appendix 5](#));
- HTA (Health Technology Assessments Database) on the Cochrane Library (1990 to present) ([Appendix 1](#));
- LILACS (Latin America and the Caribbean) (1982 to present) ([Appendix 6](#));
- ClinicalTrials.gov (<http://clinicaltrials.gov/>) ([Appendix 7](#));
- the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/) ([Appendix 8](#));
- OpenGrey (<http://opengrey.eu/>) ([Appendix 9](#)).

We will present the search strategy for each electronic sources in the Appendices of the review.

Searching other resources

We will try to identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included trials, reviews, meta-analyses, and health technology assessment reports. We will contact producers/manufacturers of all currently available anticholinergics and alpha-blockers to identify ongoing

or unpublished trials. We will search the abstracts of relevant meetings of the AUA (<http://auanet.org/>) and the International Continence Society (<http://ics.org>) of the last three years.

Data collection and analysis

Selection of studies

We will use reference management software to identify and remove potential duplicate records ([EndNote 2016](#)). Two review authors (RP, XYZ) will independently assess the titles, abstract, or both, of records we identify from the literature searches against the predefined inclusion criteria to determine which studies to assess further. Two review authors (RP, XYZ) will investigate all potentially relevant records as full-text articles, will map records to studies, and classify studies as either included studies, excluded studies, studies awaiting classification, or ongoing studies in accordance with the criteria for each provided in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)). We will resolve any discrepancies through discussion or arbitration by a third review author (XLW). If resolution of a disagreement is not possible, we will designate the study as 'awaiting classification' and we will contact the study authors for clarification. We will document the reasons for exclusion of studies that may have reasonably been expected to be included in the review in a 'Characteristics of excluded studies' table. We will present an adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram to show the process of study selection ([Liberati 2009](#)).

If any records identified in the search are reported in languages other than English or Chinese, we will obtain translation assistance to English or Chinese to enable assessment.

Data extraction and management

We will develop a dedicated data abstraction form that we will test ahead of time.

For studies that fulfill inclusion criteria, two review authors (RP, XYZ) will independently abstract the following information, which we will provide in the 'Characteristics of included studies' table:

- study design;
- study dates (if dates are not available then this will be reported as such);
- study settings and country;
- participant inclusion and exclusion criteria;
- participant details, baseline demographics;
- the number of participants by study and by study arm;
- details of relevant experimental and comparator interventions such as dose, route, frequency, and duration;
- definitions of relevant outcomes, and method and timing of outcome measurement as well as any relevant subgroups;

- study funding sources;
- declarations of interest by primary investigators.

We will extract outcomes data relevant to this Cochrane review as needed for calculation of summary statistics and measures of variance. For dichotomous outcomes, we will attempt to obtain numbers of events and totals for population of a 2 x 2 table, as well as summary statistics with corresponding measures of variance. For continuous outcomes, we will attempt to obtain means and standard deviations or data necessary to calculate this information. We will resolve any disagreements by discussion, or, if required, we will consult a third review author (XLW). We will provide information, including trial identifier, about potentially relevant ongoing studies in the 'Characteristics of ongoing studies' table. We will attempt to contact authors of included studies to obtain key missing data as needed.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary study, we will maximize the yield of information by mapping all publications to unique studies and collating all available data. We will use the most complete dataset aggregated across all known publications. In case of doubt, we will give priority to the publication that reports the longest follow-up associated with our primary or secondary outcomes.

Assessment of risk of bias in included studies

Two review authors (XLW, BW) will independently assess the risk of bias of each included study. We will resolve disagreements by consensus, or we will consult a third review author (RP). We will assess the risk of bias of each included study using Cochrane's 'Risk of bias' assessment tool (Higgins 2011b). We will assess the following domains:

- random sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias);
- incomplete outcome data (attrition bias);
- selective reporting (reporting bias);
- other sources of bias.

We will judge 'Risk of bias' domains as either 'low risk', 'high risk', or 'unclear risk' and will evaluate individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We will present a 'Risk of bias' summary figure to illustrate these findings.

For performance bias (blinding of participants and personnel) and detection bias (blinding of outcome assessment), we will evaluate the risk of bias separately for each outcome, and we will group outcomes according to whether the assessment is subjective or objective when we report our findings in the 'Risk of bias' tables.

We will also assess attrition bias (incomplete outcome data) on an outcome-specific basis, and will group outcomes with like judgments when we report our findings in the 'Risk of bias' tables.

We will further summarize the risk of bias across domains for each outcome in each included study, as well as across studies and domains for each outcome.

We define the following endpoints as subjective outcomes:

- change in IPSS;
- change in QOL.

We define the following endpoints as objective outcomes:

- incidence of adverse effect;
- incidence of acute urinary retention;
- incidence of need for surgical intervention;
- change in the Qmax;
- change in the PVR.

Measures of treatment effect

We will analyze the data using Review Manager (RevMan) software (RevMan 2014). We will express dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs). We will express continuous data as mean differences (MDs) with 95% CIs unless different studies use different measures to assess the same outcome, in which case we will express data as standardized mean differences (SMDs) with 95% CIs.

Unit of analysis issues

The unit of analysis will be the individual participant. Should we identify trials with more than two intervention groups for inclusion in the review, we will handle these in accordance with guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c).

Dealing with missing data

We will obtain missing data from study authors, if feasible, and will perform intention-to-treat (ITT) analyses if data are available; we will otherwise perform available-case analyses. We will investigate attrition rates, e.g. drop-outs, losses to follow-up, and withdrawals, and will critically appraise issues of missing data. We will not impute missing data.

Assessment of heterogeneity

In the event of excessive heterogeneity that is unexplained by subgroup analyses, we will not report outcome results as the pooled effect estimate in a meta-analysis but will provide a narrative description of the results of each study.

We will assess the heterogeneity (inconsistency) of included studies using the Chi² test, and we will consider a P value of less than 0.10

as statistically significant heterogeneity. Furthermore, we will measure the quantity of inconsistency using the I^2 statistic (Higgins 2003). We will interpret the I^2 statistic as follows:

- 0% to 40%, may not be important;
- 30% to 60%, represents moderate heterogeneity;
- 50% to 90%, represents substantial heterogeneity;
- 75% to 100%, represents considerable heterogeneity.

When we find heterogeneity, we will attempt to determine the possible reasons for it by examining individual study and subgroup characteristics.

Assessment of reporting biases

We will attempt to obtain study protocols to assess for selective outcome reporting.

If we include 10 studies or more that investigate a particular outcome, we will use funnel plots to assess small study effects. Several explanations can be offered for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials), and publication bias. We will therefore interpret results carefully.

Data synthesis

Unless there is good evidence for homogeneous effects across studies, we will summarize the data using a random-effects model. We will interpret random-effects meta-analyses with due consideration of the whole distribution of effects. In addition, we will perform statistical analyses according to the statistical guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). For dichotomous outcomes, we will use the Mantel-Haenszel method; for continuous outcomes, we will use the inverse variance method. We will use RevMan software to perform analyses (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

We expect the following characteristics to introduce clinical heterogeneity, and plan to perform subgroup analyses and investigate interactions:

- age (less than 65 years versus ≥ 65 years);
- serum prostate-specific antigen (PSA) level (< 1.3 ng/mL versus ≥ 1.3 ng/mL);
- IPSS (moderate (eight to 19) versus severe (20 to 35)).

Based on literature in this field (Kozminski 2015), the important characteristics to analyze in LUTS secondary to BPO include age, PSA level, and the IPSS.

The results from a secondary analysis of Medical Therapy of Prostatic Symptoms (MTOPS) data show that age, PSA level, and

the IPSS significantly correlate with the progression of LUTS secondary to BPO (Kozminski 2015). Additionally, Roehrborn 2008 suggested that men with PSA levels of less than 1.3 ng/mL (smaller prostates) might profit more from anticholinergic drugs.

We will use the test for subgroup differences in RevMan to compare subgroup analyses if there are a sufficient number of included studies (RevMan 2014).

Sensitivity analysis

We plan to perform sensitivity analyses in order to explore the influence of the following factors (when applicable) on effect sizes:

- restricting the analysis by taking into account risk of bias, by exclusion of studies at 'high risk' or 'unclear risk'. We will define studies at 'high risk' or 'unclear risk' of bias as trials with three or more 'Risk of bias' domains that we judge to be at high risk or unclear risk of bias.

'Summary of findings' table

We will present the overall quality of the evidence for each outcome according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which takes into account five criteria related to internal validity (risk of bias, inconsistency, imprecision, publication bias) and also to external validity, such as directness of results (Guyatt 2008). For each comparison, two review authors (XLW, BW) will independently assess the quality of the evidence for each outcome as either 'high', 'moderate', 'low', or 'very low' using the GRADEpro Guideline Development Tool (GDT) (GRADEpro GDT). We will resolve any discrepancies by consensus, or, if needed, by arbitration by a third review author (RP). For each comparison, we will present a summary of the evidence for the main outcomes in a 'Summary of findings' table, which provides key information about the best estimate of the magnitude of the effect in relative terms and absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of the overall confidence in effect estimates for each outcome (Guyatt 2011; Schünemann 2011). If meta-analysis is not possible, we will present the results in a narrative 'Summary of findings' table.

ACKNOWLEDGEMENTS

We thank Dr Weina Peng and Dr Changhe Yu for helping us to revise the search strategies. We also acknowledge Molly M Neuberger, Managing Editor, and Dr Philipp Dahm, Co-ordinating Editor, of the Cochrane Urology Group for their help and editorial support.

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- * Indicates the major publication for the study

APPENDICES

Appendix 1. Cochrane Library search strategy

1. MeSH descriptor Lower Urinary Tract Symptoms explode all trees
2. MeSH descriptor Urination Disorders explode all trees
3. LUTS
4. (urinary OR bladder OR urethra* OR urination OR LUT) NEAR/3 (symptom* OR complain*)
5. frequency OR urgency OR nocturia OR hesitancy
6. MeSH descriptor Prostatic Hyperplasia explode all trees
7. prostat* NEAR/3 (hyper* OR obstruct* OR enlarge*)
8. BPO OR BPH OR BPE
9. 1 OR 2 OR 3 OR 4 OR 5
10. 6 OR 7 OR 8
11. 9 AND 10
12. MeSH descriptor Urological Agents explode all trees
13. MeSH descriptor Adrenergic Alpha-antagonists explode all trees
14. MeSH descriptor Sulfonamides explode all trees
15. MeSH descriptor Quinazolines explode all tree
16. MeSH descriptor Doxazosin explode all tree
17. alpha NEAR/4 (block* OR antagonist*)
18. doxazosin OR alfuzosin OR silodosin OR tamsulosin OR terazosin OR naftopidil OR phenoxybenzamine OR prazosin OR indoramin
19. 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18
20. MeSH descriptor Cholinergic Antagonists explode all trees
21. MeSH descriptor Benzhydryl Compounds explode all trees
22. MeSH descriptor Quinuclidines explode all trees
23. (muscarinic OR ((M OR M1 OR M3 OR M4) NEAR receptor*) OR mAChR*) NEAR/4 (block* OR antagonist*)
24. cholinergic NEAR/4 (antagonist* or block*)
25. anticholinergic* OR antimuscarinic*
26. fesoterodine OR tolterodine OR darifenacin OR oxybutynin OR propiverine OR solifenacin OR trospium
27. 12 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26
28. 19 AND 27
29. 11 AND 28

Appendix 2. MEDLINE (via PubMed) search strategy

- #1 randomized controlled trial [pt]
- #2 controlled clinical trial [pt]
- #3 randomized [tiab]
- #4 placebo [tiab]
- #5 drug therapy [sh]
- #6 randomly [tiab]
- #7 trial [tiab]
- #8 groups [tiab]
- #9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
- #10 animals [mh] NOT humans [mh]
- #11 #9 NOT #10
- #12 Lower Urinary Tract Symptoms [mh]
- #13 Urination Disorders [mh]
- #14 LUTS [tw]
- #15 ((urinary OR bladder OR urethra* OR urination OR LUT) AND (symptom* OR complain*)) [tw]

#16 (frequency OR urgency OR nocturia OR hesitancy) [tw]
 #17 Prostatic Hyperplasia [mh]
 #18 (prostat* AND (hyper* OR obstruct* OR enlarge*)) [tw]
 #19 (BPO OR BPH OR BPE) [tw]
 #20 #12 OR #13 OR #14 OR #15 OR #16
 #21 #17 OR #18 OR #19
 #22 #20 AND #21
 #23 Urological Agents [mh]
 #24 Adrenergic Alpha-antagonists [mh]
 #25 Sulfonamides [mh]
 #26 Quinazolines [mh]
 #27 Doxazosin [mh]
 #28 (alpha AND (block* OR antagonist*)) [tw]
 #29 (doxazosin OR alfuzosin OR silodosin OR tamsulosin OR terazosin OR naftopidil OR phenoxybenzamine OR prazosin OR indoramin) [tw]
 #30 #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29
 #31 Cholinergic Antagonists [mh]
 #32 Benzhydryl Compounds [mh]
 #33 Quinuclidines [mh]
 #34 ((muscarinic OR ((M OR M1 OR M3 OR M4) AND receptor*) OR mAChR*) AND (block* OR antagonist*)) [tw]
 #35 (cholinergic AND (antagonist* or block*)) [tw]
 #36 (anticholinergic* OR antimuscarinic*) [tw]
 #37 (fesoterodine OR tolterodine OR darifenacin OR oxybutynin OR propiverine OR solifenacin OR trospium) [tw]
 #38 #23 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37
 #39 #30 AND #38
 #40 #22 AND #39
 #41 #11 AND #40

Appendix 3. EMBASE (via Elsevier) search strategy

1. exp randomized controlled trial/
 2. exp clinical trial/
 3. exp randomization/
 4. exp placebo/
 5. exp control group/
 6. (random\$ OR place\$ OR group\$).tw
 7. (clin\$ adj3 trial\$).tw
 8. ((singl\$ OR doubl\$ OR tripl\$ OR trebl\$) adj3 (blind\$ OR mask\$)).tw
 9. (animal OR animal experiment).sh
 10. human.sh
 11. 9 NOT 10
 12. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
 13. 12 NOT 11
 14. exp Lower Urinary Tract Symptoms/
 15. exp Micturition Disorder/
 16. LUTS.tw
 17. ((urinary or bladder or urethra\$ or urination or LUT) adj3 (symptom\$ or complain\$)).tw
 18. (frequency OR urgency OR nocturia OR hesitancy).tw
 19. exp prostate hypertrophy/
 20. (prostat* adj3 (hyper* or obstruct* or enlarge*)).tw
 21. (BPO OR BPH OR BPE).tw
 22. 14 OR 15 OR 16 OR 17 OR 18

23. 19 OR 20 OR 21
24. 22 AND 23
25. exp alpha adrenergic receptor blocking agent/
26. (alpha adj4 (antagonist\$ OR block\$)).tw
27. (doxazosin OR alfuzosin OR silodosin OR tamsulosin OR terazosin OR naftopidil OR phenoxybenzamine OR prazosin OR indoramin).tw
28. exp cholinergic receptor blocking agent/
29. (muscarinic OR ((M OR M1 OR M3 OR M4) adj receptor*) OR mAChR*) adj4 (block* OR antagonist*).tw
30. cholinergic adj4 (antagonist* or block*).tw
31. (anticholinergic* OR antimuscarinic*).tw
32. (fesoterodine OR tolterodine OR darifenacin OR oxybutynin OR propiverine OR solifenacin OR trospium).tw
33. 25 OR 26 OR 27
34. 28 OR 29 OR 30 OR 31 OR 32
35. 33 AND 34
36. 24 AND 35
37. 13 AND 36

Appendix 4. Web of Science search strategy

1. TS=clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS= follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*)
2. TS=(“lower urinary tract symptom*” OR frequency OR urgency OR nocturia OR hesitancy OR LUTS)
3. TS=((urinary OR bladder OR urethra* OR urination OR LUT) NEAR/3 (symptom* OR complain*))
4. TS=(prostat* NEAR/3 (hyper* OR obstruct* OR enlarge*))
5. TS=(BPO OR BPH OR BPE)
6. TS=(alpha NEAR/4 (block* OR antagonist*))
7. TS=(doxazosin OR alfuzosin OR silodosin OR tamsulosin OR terazosin OR naftopidil OR phenoxybenzamine OR prazosin OR indoramin)
8. TS= ((muscarinic OR ((M OR M1 OR M3 OR M4) NEAR receptor*) OR mAChR*) NEAR/4 (block* OR antagonist*))
9. TS=(cholinergic NEAR/4 (antagonist* or block*))
10. TS=(anticholinergic* OR antimuscarinic* OR fesoterodine OR tolterodine OR darifenacin OR oxybutynin OR propiverine OR solifenacin OR trospium)
11. #2 OR #3
12. #4 OR #5
13. #6 OR #7
14. #8 OR #9 OR #10
15. #11 AND #12
16. #13 AND #14
17. #1 AND #16

Appendix 5. Chinese Biomedical Literature Database (via SinoMed) search strategy

- #1 主题词==“随机对照试验/全部副主题”
- #2 主题词==“随机对照试验/全部副主题”
- #3 主题词==“随机分配”
- #4 主题词==“双盲法”
- #5 主题词==“单盲法”
- #6 单盲OR 双盲 OR 三盲 OR 盲法 OR安慰剂 OR 随机
- #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6

#8 动物 in CT
 #9 人类 in CT
 #10 #8 NOT #9
 #11 #7 NOT #10
 #12 主题词==“下尿路症状/全部副主题”
 #13 下尿路症状 OR 尿频 OR 尿急 OR 排尿等待 OR 排尿困难 OR 排尿费力 OR 夜尿 OR 尿滴沥
 #14 主题词==“前列腺增生/全部副主题”
 #15 前列腺肥大 OR 前列腺梗阻 OR 前列腺疾病 OR 前列腺增生
 #16 #12 OR #13
 #17 #14 OR #15
 #18 #16 AND #17
 #19 主题词==“肾上腺素受体阻断药/全部副主题”
 #20 肾上腺素 AND 受体AND(拮抗 OR 阻断)
 #21 特拉唑嗪 OR 阿呋唑嗪 OR 坦索罗辛 OR 多沙唑嗪 OR 哌唑嗪 OR 赛洛多辛 OR 酚苳明 OR 哌唑嗪 OR 酚妥拉明
 #22 主题词==“胆碱能受体阻断药/全部副主题”
 #23(胆碱能 OR M OR M1 OR M3 or M4) AND 受体AND(拮抗 OR 阻断)
 #24 托特罗定 OR 索利那新 OR 奥昔布宁 OR 非索罗定 OR 达非那新 OR 丙哌维林 OR 曲司氯铵
 #25 #19 OR #20 OR #21
 #26 #22 OR #23 OR #24
 #27 #25 AND #26
 #28 #18 AND #27
 #29 #11 AND #28

Appendix 6. LILACS search strategy

(mh:("Prostatic Hyperplasia")) OR (ti:("prostatic hyperplasia")) OR (ab:("prostatic hyperplasia")) OR (ti:("prostatic obstruction")) OR (ab:("prostatic obstruction")) OR (ti:("prostatic enlargement")) OR (ab:("prostatic enlargement")) OR (ti:("BPH")) OR (ab:("BPH")) OR (ti:("BPO")) OR (ab:("BPO")) OR (ti:("BPE")) OR (ab:("BPE")) AND db:("LILACS") AND type_of_study:("clinical_trials") RCTs filter:
 ((PT:"ensayo clinico controlado aleatorio" OR PT:"ensayo clinico controlado" OR PT:"estudio multicéntrico" OR MH:"ensayos clinicos controlados aleatorios como asunto" OR MH:"ensayos clinicos controlados como asunto" OR MH:"estudios multicéntricos como asunto" OR MH:"distribución aleatoria" OR MH:"método doble ciego" OR MH:"metodo simple-ciego") OR ((ensaio\$ OR ensayo\$ OR trial\$) AND (azar OR acaso OR placebo OR control\$ OR aleat\$ OR random\$ OR enmascarado\$ OR simpleciego OR ((simple\$ OR single OR duplo\$ OR doble\$ OR double\$) AND (cego OR ciego OR blind OR mask))) AND clinic\$)) AND NOT (MH:animales OR MH:conejos OR MH:ratones OR MH:ratas OR MH:primates OR MH:perros OR MH:gatos OR MH:porcos OR PT:"in vitro")

Appendix 7. ClinicalTrials.gov (advanced search)

Search Terms: (lower urinary tract symptoms OR LUTS OR urinary symptom OR “urinary symptoms” OR “urinary complain” OR “urinary complains” OR bladder symptom OR “bladder symptoms” OR “bladder complain” OR “bladder complains” OR “urethra symptom” OR “urethra symptoms” OR “urethral symptom” OR “urethral symptoms” OR “urethra complain” OR “urethra complains” OR urethral complain OR “urethral complains” OR urination symptom OR “urination symptoms” OR “urination complain” OR “urination complains OR frequency OR urgency OR nocturia OR hesitancy) AND (prostate hyperplasia OR prostate obstruction OR prostate enlargement OR prostatic hyperplasia OR prostatic obstruction OR prostatic enlargement OR BPH OR BPE OR BPO)

Study Type: Interventional Studies

Interventions: (alpha blocker OR alpha blockers OR alpha antagonist OR alpha antagonists OR doxazosin OR alfuzosin OR silodosin OR tamsulosin OR terazosin OR naftopidil OR phenoxybenzamine OR prazosin OR indoramin) AND (cholinergic blocker OR cholinergic blockers OR cholinergic antagonist OR cholinergic antagonists OR muscarinic blocker OR muscarinic blockers OR muscarinic antagonist OR muscarinic antagonists OR anticholinergics OR muscarinics OR fesoterodine OR tolterodine OR darifenacin OR oxybutynin OR propiverine OR solifenacin OR trospium)

Appendix 8. World Health Organization International Clinical Trials Registry Platform Search Portal (standard search)

(to be run as one search string)

prostat* hyper* AND doxazosin OR
prostat* hyper* AND alfuzosin OR
prostat* hyper* AND silodosin OR
prostat* hyper* AND tamsulosin OR
prostat* hyper* AND terazosin OR
prostat* hyper* AND naftopidil OR
prostat* hyper* AND phenoxybenzamine OR
prostat* hyper* AND prazosin OR
prostat* hyper* AND indoramin OR
prostat* hyper* AND fesoterodine OR
prostat* hyper* AND tolterodine OR
prostat* hyper* AND darifenacin OR
prostat* hyper* AND oxybutynin OR
prostat* hyper* AND propiverine OR
prostat* hyper* AND solifenacin OR
prostat* hyper* AND trospium OR
prostat* obstruct* AND doxazosin OR
prostat* obstruct* AND alfuzosin OR
prostat* obstruct* AND silodosin OR
prostat* obstruct* AND tamsulosin OR
prostat* obstruct* AND terazosin OR
prostat* obstruct* AND naftopidil OR
prostat* obstruct* AND phenoxybenzamine OR
prostat* obstruct* AND prazosin OR
prostat* obstruct* AND indoramin OR
prostat* obstruct* AND fesoterodine OR
prostat* obstruct* AND tolterodine OR
prostat* obstruct* AND darifenacin OR
prostat* obstruct* AND oxybutynin OR
prostat* obstruct* AND propiverine OR
prostat* obstruct* AND solifenacin OR
prostat* obstruct* AND trospium OR
prostat* enlarge* AND doxazosin OR
prostat* enlarge* AND alfuzosin OR

prostat* enlarge* AND silodosin OR
 prostat* enlarge* AND tamsulosin OR
 prostat* enlarge* AND terazosin OR
 prostat* enlarge* AND naftopidil OR
 prostat* enlarge* AND phenoxybenzamine OR
 prostat* enlarge* AND prazosin OR
 prostat* enlarge* AND indoramin OR
 prostat* enlarge* AND fesoterodine OR
 prostat* enlarge* AND tolterodine OR
 prostat* enlarge* AND darifenacin OR
 prostat* enlarge* AND oxybutynin OR
 prostat* enlarge* AND propiverine OR
 prostat* enlarge* AND solifenacin OR
 prostat* enlarge* AND trespium OR
 BPH AND doxazosin OR
 BPH AND alfuzosin OR
 BPH AND silodosin OR
 BPH AND tamsulosin OR
 BPH AND terazosin OR
 BPH AND naftopidil OR
 BPH AND phenoxybenzamine OR
 BPH AND prazosin OR
 BPH AND indoramin OR
 BPH AND fesoterodine OR
 BPH AND tolterodine OR
 BPH AND darifenacin OR
 BPH AND oxybutynin OR
 BPH AND propiverine OR
 BPH AND solifenacin OR
 BPH AND trespium OR
 BPO AND doxazosin OR
 BPO AND alfuzosin OR
 BPO AND silodosin OR
 BPO AND tamsulosin OR
 BPO AND terazosin OR
 BPO AND naftopidil OR
 BPO AND phenoxybenzamine OR
 BPO AND prazosin OR
 BPO AND indoramin OR
 BPO AND fesoterodine OR
 BPO AND tolterodine OR
 BPO AND darifenacin OR
 BPO AND oxybutynin OR
 BPO AND propiverine OR
 BPO AND solifenacin OR
 BPO AND trespium OR
 BPE AND doxazosin OR
 BPE AND alfuzosin OR
 BPE AND silodosin OR
 BPE AND tamsulosin OR
 BPE AND terazosin OR
 BPE AND naftopidil OR
 BPE AND phenoxybenzamine OR

BPE AND prazosin OR
BPE AND indoramin OR
BPE AND fesoterodine OR
BPE AND tolterodine OR
BPE AND darifenacin OR
BPE AND oxybutynin OR
BPE AND propiverine OR
BPE AND solifenacin OR
BPE AND trospium OR

Appendix 9. OpenGrey search strategy

(lower urinary tract symptoms OR LUTS OR urinary symptom* OR urinary complain* OR bladder symptom* OR bladder complain* OR urethra* symptom* OR urethra* complain* OR urination symptom* OR frequency OR urgency OR nocturia OR hesitancy) AND (prostat* hyper* OR prostat* obstruct* OR prostat* enlarge* OR BPH OR BPE OR BPO) AND (alpha blocker* OR alpha antagonist* OR doxazosin OR alfuzosin OR silodosin OR tamsulosin OR terazosin OR naftopidil OR phenoxybenzamine OR prazosin OR indoramin) AND (cholinergic blocker* OR cholinergic antagonist* OR muscarinic blocker* OR muscarinic antagonist* OR anticholinergics OR muscarinics OR fesoterodine OR tolterodine OR darifenacin OR oxybutynin OR propiverine OR solifenacin OR trospium)

CONTRIBUTIONS OF AUTHORS

R Pang conceived, designed and wrote the protocol.

X-Y Zhou developed and wrote the protocol.

B Wang developed the protocol.

X-l Wang developed the protocol.

X-L Yin developed the protocol.

H Bo developed the protocol.

DECLARATIONS OF INTEREST

R Pang: none known.

X-Y Zhou: none known.

B Wang: none known.

X-l Wang: none known.

X-L Yin: none known.

H Bo: none known.

SOURCES OF SUPPORT

Internal sources

- Guang An Men Hospital, China Academy of Chinese Medical Sciences, China.

This work was funded by grant 2014S292 partly.

External sources

- Beijing Municipal Science & Technology Commission, China.

This work was funded partly by Beijing Municipal Science & Technology Commission No. Z161100000516156.

NOTES

We based parts of the [Methods](#) section of this protocol on a standard template developed by the Cochrane Metabolic and Endocrine Disorders Group, which the Cochrane Urology Group has modified and adapted for use.